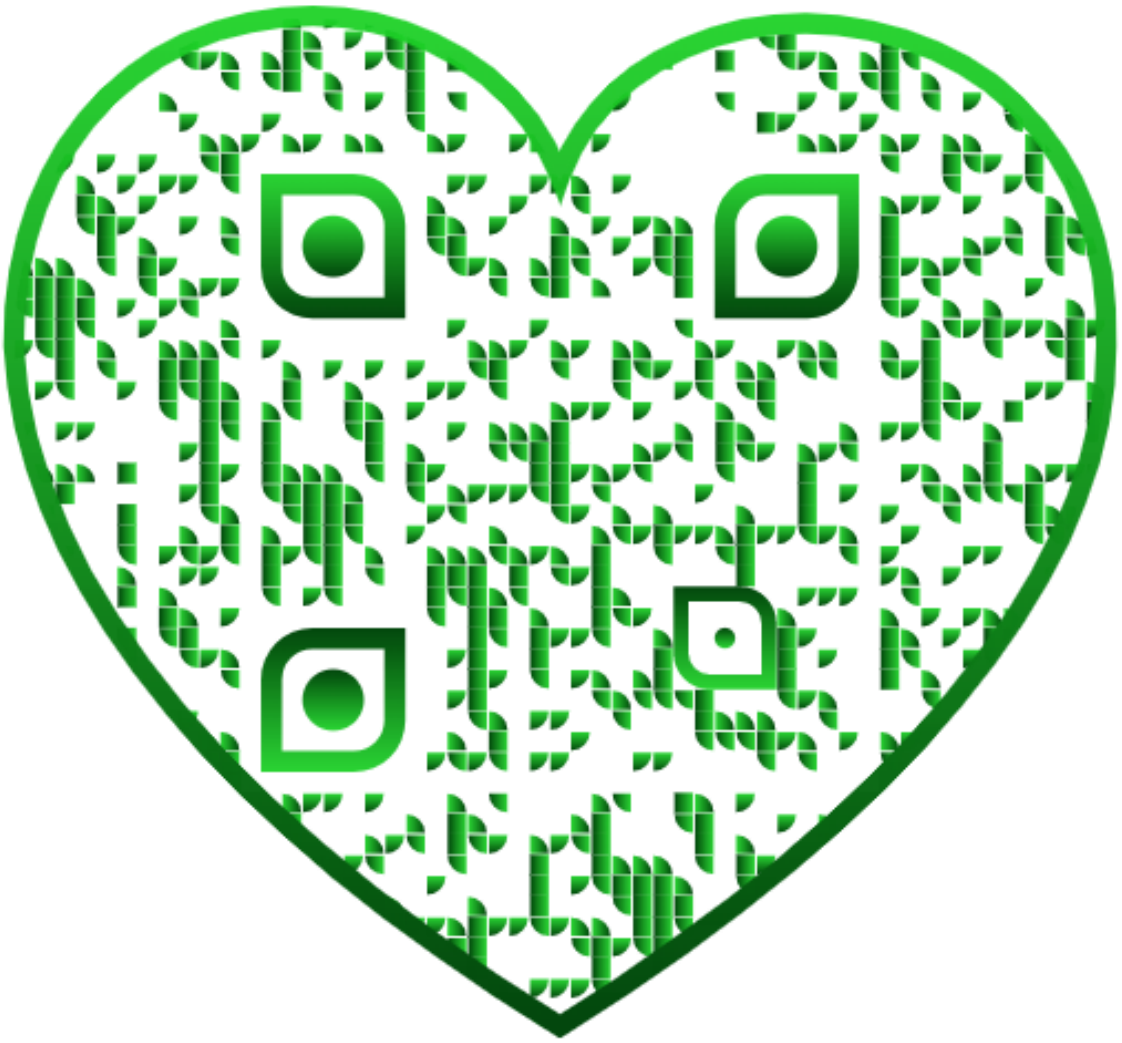
1. Introduction

- Definitions
- Barriers of drug transport
- Mechanisms of drug transport



Introduction, Definition of terms

- **Biopharmaceutics**
  - Deals with the interrelationship between: the physicochemical properties of a drug, the dosage form in which the drug is given, and the route of administration on the rate and extent of systemic drug absorption.
- **Pharmacokinetics**
  - Concerned with time course of drug absorption, distribution and elimination (ADME).

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- **Pharmacodynamics**
  - Concerned with relationship between concentration of drug at site of action and clinical response.
- **Bioavailability**
  - BA is the fraction of an administered dose of unchanged drug that reaches the systemic circulation.
- **Bioequivalence**
  - A term used to assess the expected *in vivo* biological equivalence of two proprietary preparations of a drug.

Concepts and applications of Biopharmaceutics

- Biopharmaceutics considers the factors that affect the rate and extent of systemic drug absorption.
- It also considers the impact of the various manufacturing methods and technologies on the intended performance of the drug product.
- For this, biopharmaceutics uses quantitative methods and theoretical models.

- The study of biopharmaceutics is based on fundamental scientific principles and experimental methodology:
  - *In vitro* (test apparatus and equipment) and
  - *In vivo* (human subjects or laboratory animals)
- Biopharmaceutics allows for rational design of drug products to deliver the drug at a specific rate to the body.
  - This will help to optimize the therapeutic effect and minimize any adverse effects.

- Knowledge of biopharmaceutics is essential for rational drug product design - based on:
  - The physical and chemical properties of the drug substance;
  - The route of drug administration, including the anatomic and physiologic nature of the application site;
  - Desired pharmacodynamic effect (e.g., immediate or prolonged activity);
  - Toxicologic properties of the drug;
  - Safety of excipients; and
  - Effect of excipients and dosage form on drug delivery.

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- In general, biopharmaceutics involves factors that influence the:
  - Protection and stability of the drug within the drug product;
  - The rate of drug release from the drug product;
  - The rate of dissolution of the drug at the absorption site; and
  - The availability of the drug at its site of action.

- The scope of biopharmaceutics is comprised of:
  - The path the drug must take from the dosage form to the site of action, and
  - The factors encountered en-route.
- Important for biopharmaceutics are:
  - The physicochemical characteristics of the API,
  - The desired drug product,
  - Considerations of the anatomy and physiology of the human body

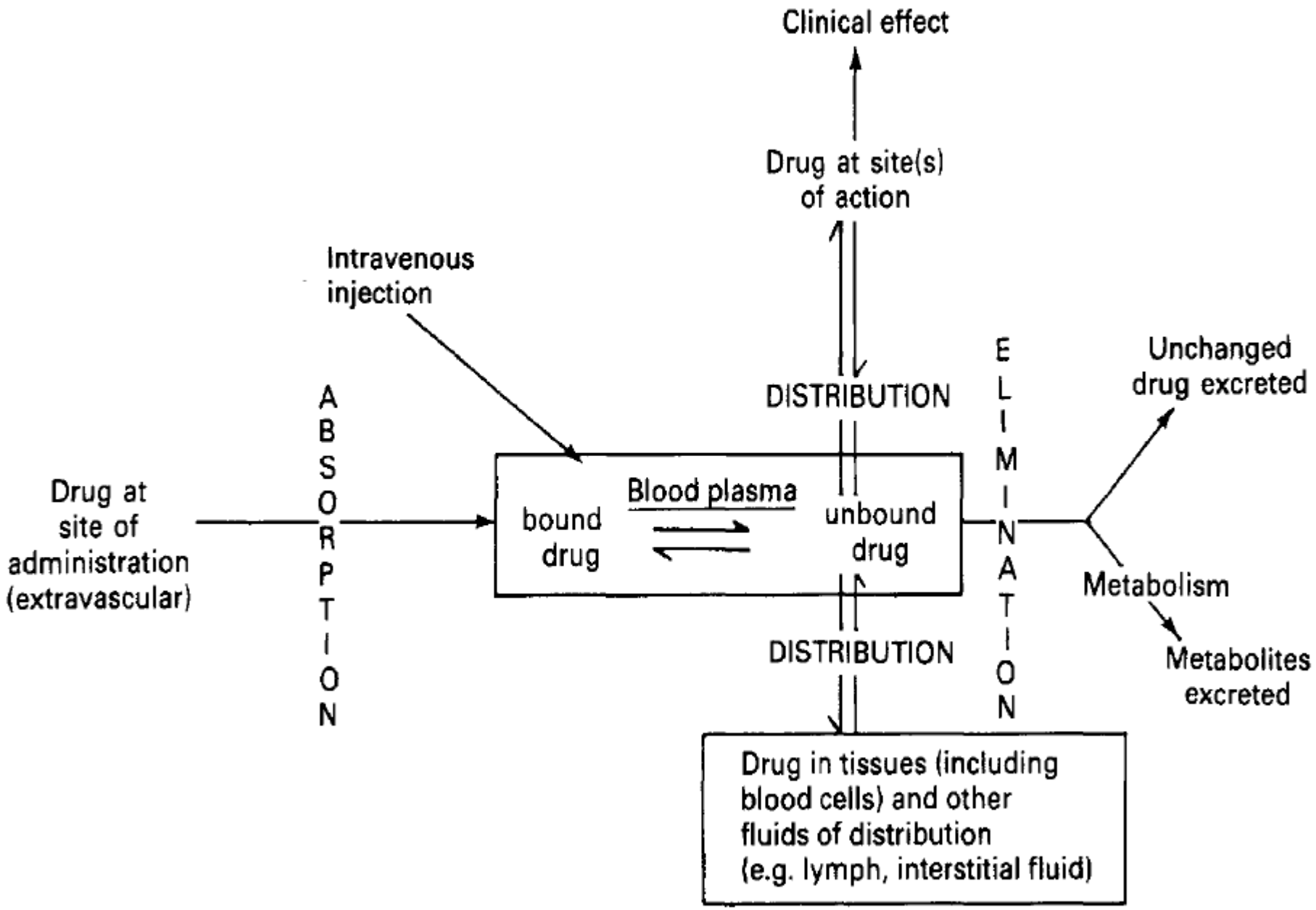

Fig. Factors that influence concentration of drug at its site(s) of action.

Introduction, Barriers of drug transport

- Drugs are better administered via **noninvasive** pathways, due to: patient compliance, safety, production costs and product stability.
  - For this, conventional oral tablet remains one of the most popular choices.
  - Issue: the drug substance is intended to permeate a barrier and act at a site distant to its dissolution site.
- The epithelial tissues of the body represent barriers for topical and systemic treatment by drug substances.
  - Internal epithelia, i.e. **endothelia**, act in addition as barriers between the systemic circulation and the target such as the brain and the posterior segments of the eye.

Epithelial cells

- Specialized cells, cover nearly all surfaces of the body (both external and internal).
- Constitute the barriers between the body and the external environment.
- Main functions:
  - Protect the internal environment of the body
  - Allow exchange of relevant nutrients.

- Epithelia can be classified morphologically by:
  - Their number of cell layers,
  - The shape of the cells, and
  - The presence of apical surface specializations such as cilia or keratin.

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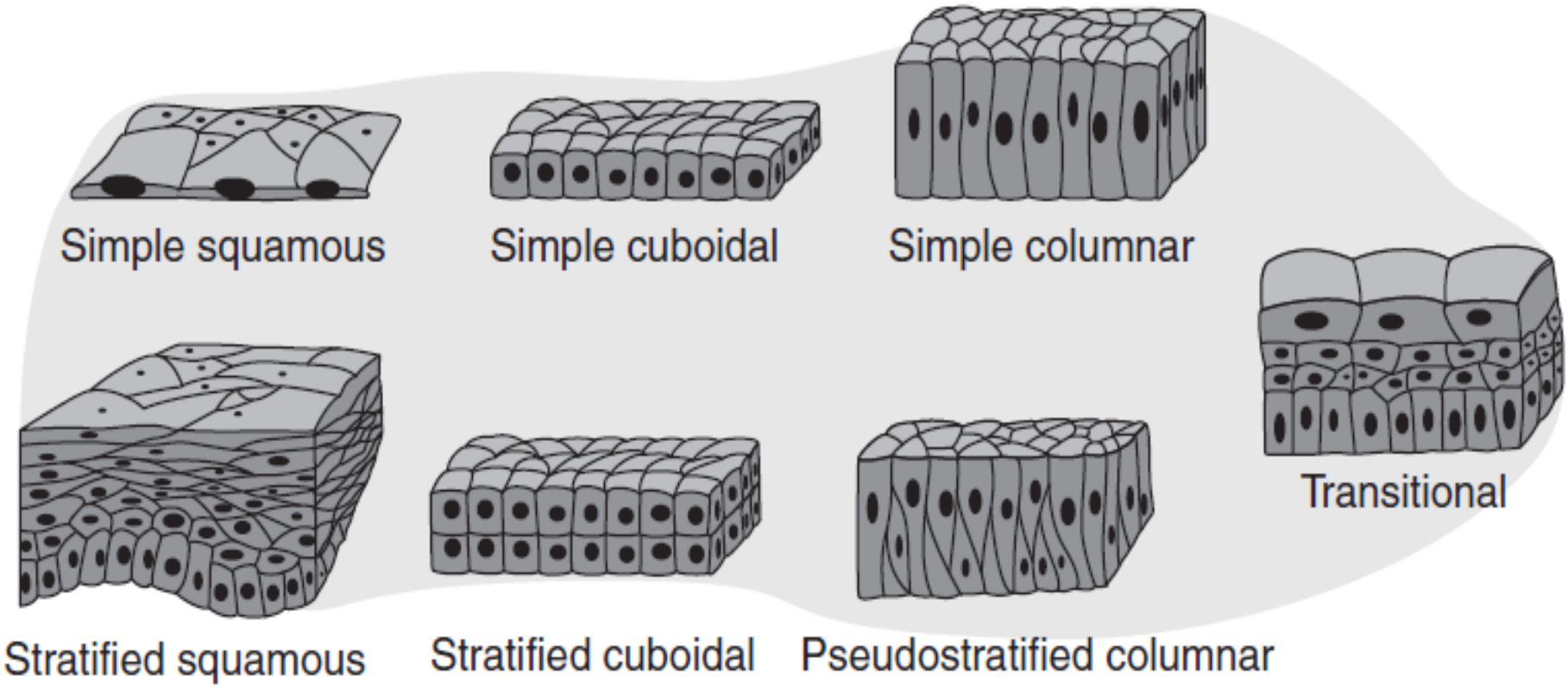
Number of cell layers	*Shape of cells*	*Specialisations*
1: Simple epithelium	Flat, irregular: squamous epithelium	Apical cilia: ciliated epithelium
>1: Stratified epithelium	Cuboidal: cuboidal epithelium	Keratin in apical layers: keratinising epithelium
	Tall columnar: columnar epithelium	

- Simple epithelia ~ absorption or secretion
- Stratified epithelia ~ protective roles
- Simple squamous epithelia ~ found lining airways, in body cavities and blood vessels, permitting passive transport of liquids and gases.
- Cuboidal epithelia ~ found in ducts and tubules of the kidney and glands.
- Columnar epithelia ~ found in highly absorptive epithelia such as the small intestine.


Simple squamous
Simple cuboidal
Simple columnar
Transitional
Stratified squamous
Stratified cuboidal
Pseudostratified columnar

- Epithelia can also be classified as '**tight**' or '**leaky**' on the basis of their resistance to paracellular water and solute flow.
  - The colon and collecting ducts of the kidney are typically tight epithelia where uptake of salts and water is transcellular.
  - The small intestine and the proximal tubule of the kidney are examples of leaky epithelia where a substantial paracellular transport can occur.
- Both tight and leaky epithelia possess tight junctions, but differ in their permeability.

- **Tight junctions**
  - Epithelial cells generate boundaries between the body and its external environment.
  - Two important features that enable epithelial cells to allow controlled passage of water, nutrients and waste products:
    - Tight junctions, and
    - Polarity of protein expression
  - Tight junctions define the border between the apical and lateral membranes, and enable polarized expression of proteins.

- Tight junctions connect epithelial cells at their apical end.
- The barrier function of epithelia is determined by:
  - Passive permeability of the tight junctions and of the epithelial cells,
  - The selective barrier properties of the cells, which are determined by a range of transport proteins.
- Tight junctions constitute a barrier for:
  - Paracellular diffusion of molecules
  - Lateral diffusion of membrane proteins within the membrane

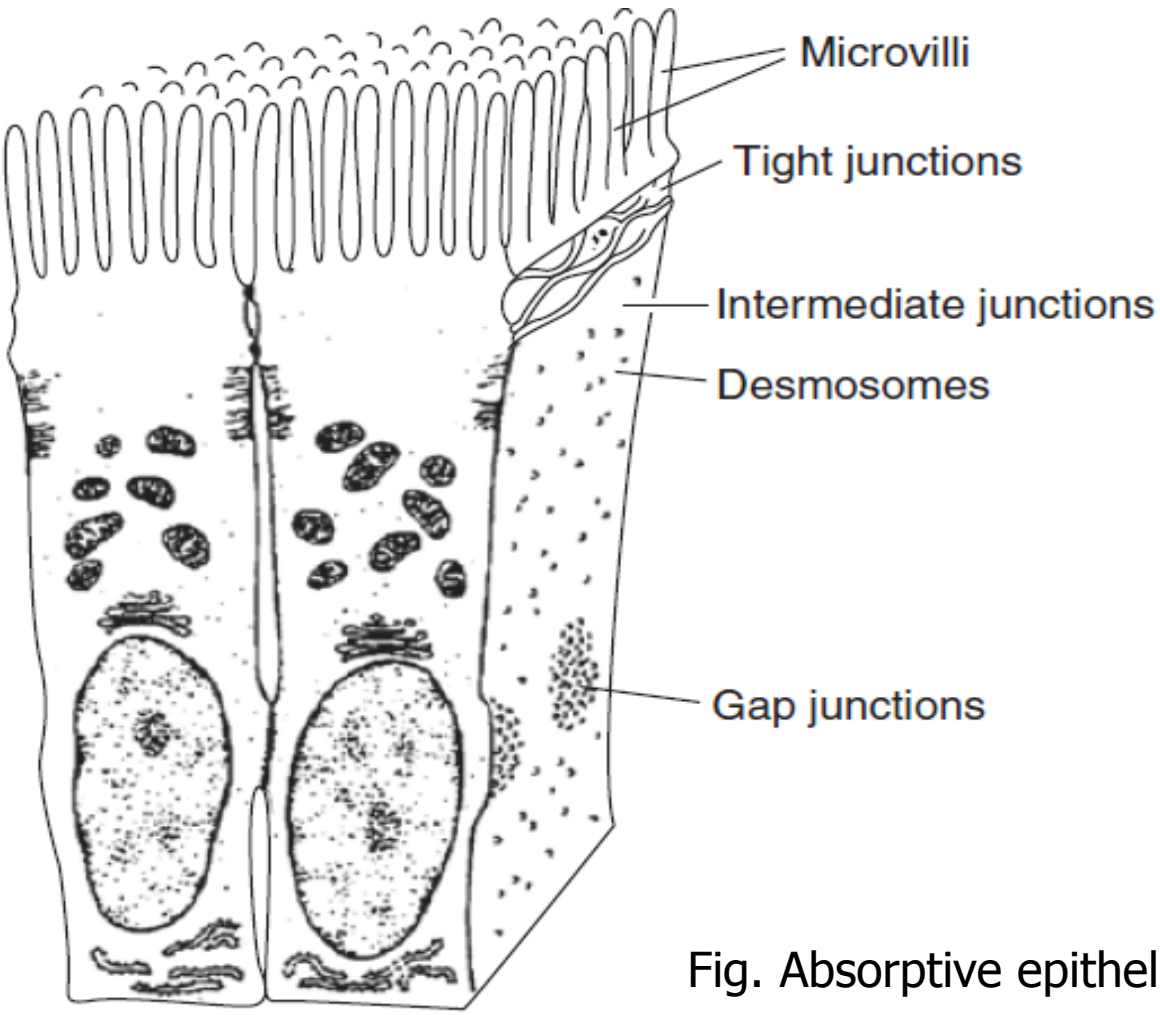


Fig. Absorptive epithelial cells.

The GI tissue barriers

- **Oral cavity**
  - The oral cavity is thus covered with stratified, squamous epithelia;
    - Functions:
      - Provide an environment for wetting and chewing
      - Maintaining a barrier for micro-organisms and
      - Protection against mechanical stress

- The oral cavity is an effective barrier for large hydrophilic molecules and micro-organisms.
- Challenges in terms of drug delivery to the oral cavity:
  - The transit time is very short
  - The continuous flow of saliva
  - Compliance problems (presence of sensory nerves)

- **The stomach**
  - The epithelium of the stomach is a simple columnar epithelium,
    - Its main role being the secretion of a protective mucus layer.
  - Specialized gland cells also produce hydrochloride and precursors of digestive enzymes.
  - Very little absorption occurs in the stomach.
  - Main role ~ control the rate of chyme influx into the small intestine.

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GI segment	*Surface area (m^2)*	*Segment length (m)*	*Residence time (h)*	*pH of segment*
Stomach	3.5	0.25	1.5	1–2
Duodenum	1.9	0.35	0.5–0.75	4–5.5
Jejunum	184.0	2.8	1.5–2.0	5.5
Ileum	276.0	4.2	5–7	7.0–7.5
Colon and rectum	1.3	1.5	1–60	7.0–7.5

- **The small intestine**
  - The small intestine is specialized in absorbing nutrients.
  - Highly folded
  - The surface is covered by small finger-like projections (villi).
  - The epithelial cells covering the villi are covered with microvilli.
  - The SI epithelium mediates absorption of dietary protein and carbohydrates via a range of membrane transport proteins.

- Advantages ~ drug absorption
  - Huge surface area,
  - Relatively long transit time, and
  - Wide range of nutrient transporters present.
- Limitations
  - Drug candidates be stable in the acidic environment of the stomach and attack from the digestive enzymes.
  - Drugs should accommodate uptake by passive diffusion, or be a substrate for one of the intestinal transporters.
  - Drugs should not readily undergo first-pass metabolism in the liver.

- **The colon and the rectum**

  - The function of the colon is to store and concentrate undigested matter and propagate the luminal content towards the rectum.

  - Absorption is mainly limited to absorption of sodium, chloride and water, but vitamins produced by colonic bacteria are also absorbed.

  - Due to the high vascularization and its accessible epithelial surface, drug substances can be taken up from the rectal lumen.

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The skin

- A continuous protective epithelium covering the external surface of the body.
- Major roles
  - Prevent water loss from the organism,
  - Provide a physical and immunological barrier against pathogens,
  - Provide protection against mechanical, chemical and thermal stimuli.

- Outer boundary of the skin is the epidermis, a squamous stratified keratinized epithelium.
- Three layers: Epidermis, Dermis, and Hypodermis.
- The epidermis is the actual barrier towards the outside environment, and it is across this cell layer that drug substance permeation must occur.
- The major challenge of drug administration via the skin is to overcome the barrier residing in the strateum corneum.

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Barriers in the brain

- The capillaries of the brain make up a very effective barrier for transport of drug substances and solutes between the blood and the cerebrospinal fluid.
- The endothelial cells of the capillaries form an extremely tight continuous monolayer.
- The presence of tight junctions makes the tissue practically impermeable for larger hydrophilic molecules.
  - With the exception of some nutrient molecules, which are transported through the cells via nutrient transporters.

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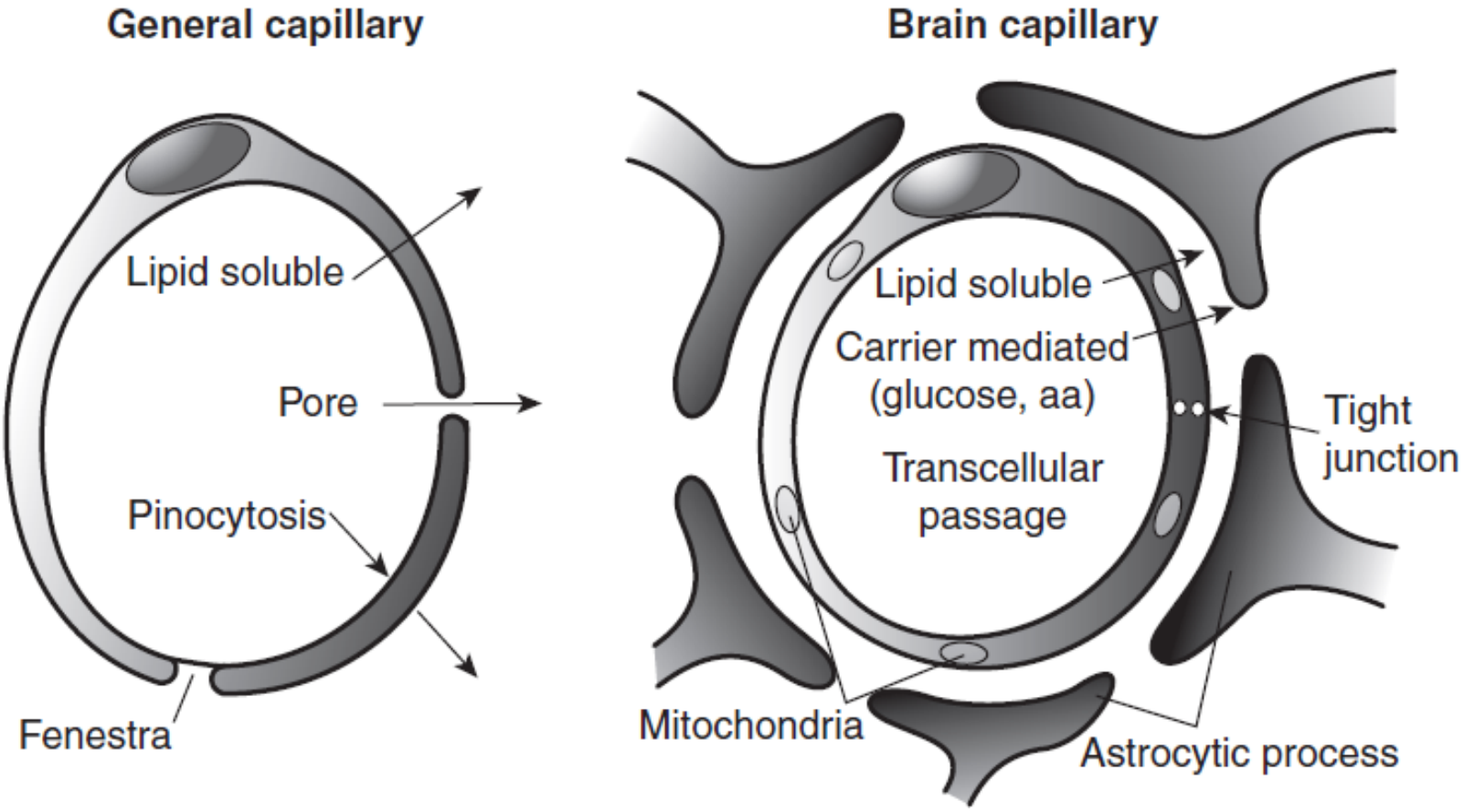
- Lipophilic molecules, which in other tissues normally would pass by simply diffusion, are extruded by the activity of efflux pumps,
  - Transport proteins situated in the apical membrane of the brain endothelial cells.
- Thus the blood–brain barrier provides
  - A 'passive' physical barrier, i.e. the tight monolayer of cells, and
  - An 'active' barrier, i.e. the efflux pumps.


General capillary
Lipid soluble
Pore
Pinocytosis
Fenestra
Brain capillary
Lipid soluble
Carrier mediated
(glucose, aa)
Transcellular
passage
Tight
junction
Mitochondria
Astrocytic process

- The blood–brain barrier is considered the most important challenge factor in the development of central nervous system (CNS) drugs.

- The extreme tightness of the blood–brain barrier and the activity of efflux proteins make administration of drug substances to the brain a great challenge.

Introduction, Mechanisms of drug transport

- Movement of molecules in solutions and molecular transport across barriers may be described mathematically,
- Knowledge about these descriptions will aid in the design of experiments and interpretation of data.

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1. Passive Diffusion

- Theoretically, a lipophilic drug may pass through the cell or go around it.

- If the drug has a low molecular weight and is lipophilic, the lipid cell membrane is not a barrier to drug diffusion and absorption.

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- Passive diffusion is the membrane transport of drugs and other chemicals directly through the lipid or aqueous channels
- By passive diffusion molecules spontaneously diffuse from a region of higher concentration to a region of lower concentration.
- It is passive because **no external energy** is expended.

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- If the two sides have the same drug concentration, forward-moving drug molecules are balanced by molecules moving back, resulting in **no net transfer** of drug.

- When one side is higher in drug concentration, at any given time, the number of forward-moving drug molecules will be higher than the number of backward-moving molecules.

- Note - Random movement of molecules is natural - because molecules possess kinetic energy and constantly collide with one another

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- Passive diffusion is the major absorption process for most drugs.
- The driving force for passive diffusion is concentration gradient on the mucosal side compared to the blood.
- This passive transport of drugs and molecules is described by the Fick's first law.

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- Fick's first law states:
  - The rate of diffusion across a membrane (dC/dt) is proportional to the difference in drug concentration on each side of the membrane (ΔC)

$$-\frac{dC}{dt} = k(C_1 - C_2)$$

$$= k\Delta C$$

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- Fick's first law for the absorption of drug from the GI lumen into the plasma can be written as:

$$-\frac{dC}{dt} = \frac{DAK}{h}(C_{GI} - C_p)$$

where dC/dt = rate of diffusion, D = diffusion coefficient, K = lipid water partition coefficient of drug, A = surface area of membrane; h = membrane thickness, and $C_{GI} - C_p$ = difference between the concentrations of drug in the GIT and in the plasma.

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- Absorption of the drug from the GIT requires:
  - Diffusion in the lumen to the gut wall and
  - Penetration of the epithelial barriers to the capillaries of the systemic circulation
- Then, the drug distributes rapidly into an apparent volume
  - This volume is considerably larger than the blood volume

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- Thus, drug concentration in the blood will be much lower than at the absorption site.
  - The general circulation functions like a sink for the drug in the GIT
- This creates a large concentration gradient (i.e. $C_{GI} \gg C_p$)

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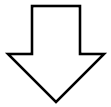
- Consequently, ΔC is nearly equal to C_{GI}
- Therefore, we can rewrite the Fick's first law equation as:

$$-\frac{dC}{dt} = \frac{DAK}{h}(C_{GI} - C_p)$$



$$-\frac{dC}{dt} = \frac{DAK}{h}C_{GI}$$

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- This last equation is a familiar form of a first-order rate equation
- The GI absorption of most drugs may be described by a first-order kinetics.
  - The rate of absorption is proportional to drug concentration over a wide concentration range – indicating passive absorption

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2. Carrier Mediated Transport

- Despite the hydrophobic nature of the cell membrane, it is necessary for a number of hydrophilic materials to enter and leave the cell.

- Drugs and other molecules can go through the intestinal epithelial cells by either diffusion or a carrier-mediated mechanism.

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- Some substances may be absorbed by simultaneous carrier mediated and passive transport.
  - The contribution of each processes to the total absorption rate varies with concentration

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- Specialized carrier-mediated transport systems are present in the body, especially in the intestine.
- Characterized by –
  - Saturation (capacity-limited process)
  - Competition (for substances with the same transfer mechanism)
  - Structural and Site specificity

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Active transport

- Active transport is a carrier-mediated trans membrane process
- It plays an important role in the GI absorption and in renal and biliary secretion of many drugs and metabolites.
- Characterized by the transport of drug **against** a concentration gradient.

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- It is an energy-consuming system
- It requires a carrier that binds the drug to form a carrier–drug complex that shuttles the drug across the membrane
- It is a saturable process
  - The rate of drug absorption increases with drug concentration until the carrier molecules are completely saturated.

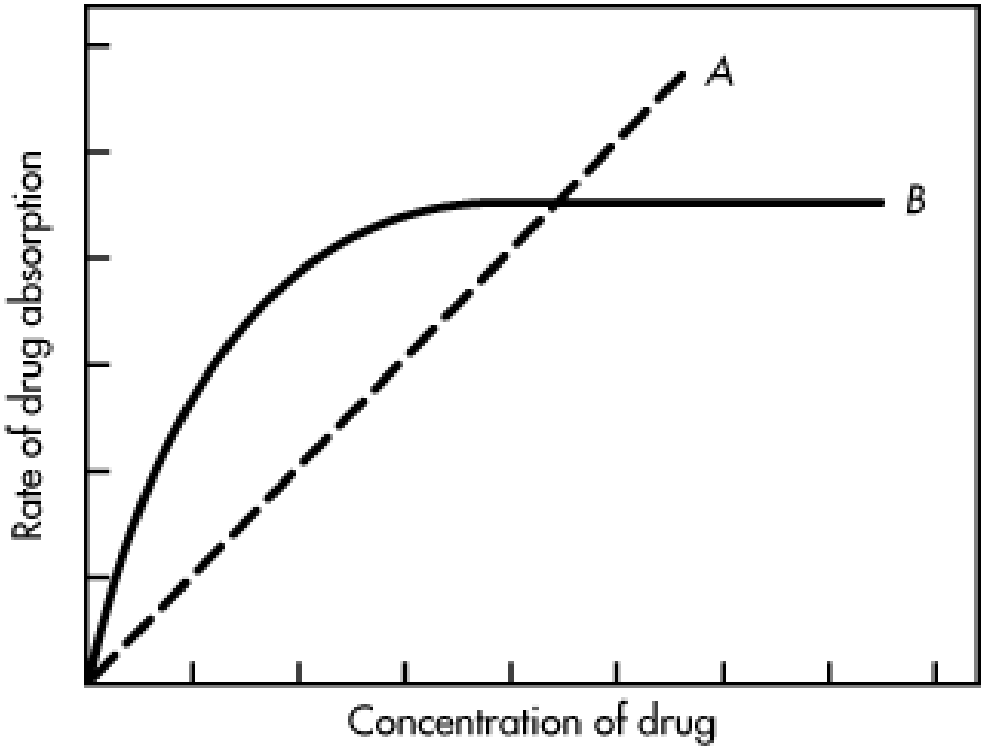

Fig. Rates of drug absorption by passive diffusion (line A) and by a carrier-mediated system (line B).

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Facilitated diffusion

- Differing from active transport in that the drug moves along a concentration gradient
- Therefore, this system does not require energy input.
- However, because this system is carrier mediated, it is saturable and structurally selective for the drug.

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Vesicular Transport

- It is the process of engulfing particles or dissolved materials by the cell.
- Pinocytosis and phagocytosis are forms of vesicular transport that differ by the type of material ingested.
- Endocytosis and exocytosis are the processes of moving specific macromolecules into and out of a cell, respectively.

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Pore (Convective) Transport

- Very small molecules (such as urea, water, and sugars) are able to cross cell membranes rapidly, as if the membrane contained channels or pores.

- A certain type of protein called a transport protein may form an open channel across the lipid membrane of the cell

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Ion-Pair Formation

- Strong electrolyte drugs are highly ionized or charged molecules.
- Such drugs maintain their charge at all physiologic pH values and penetrate membranes poorly.
- When these drugs linked up with an oppositely charged ion, an ion pair is formed in which the overall charge of the pair is neutral.